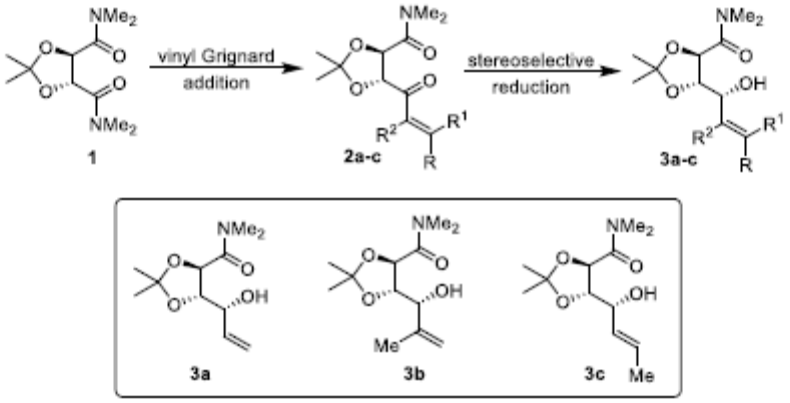
SYNOPSIS

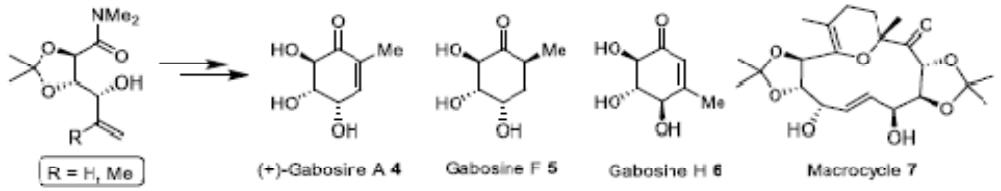
The thesis entitled "***Total synthesis of bio-active natural products gabosines, crassalactone C, anamarine and iriomoteolide 3a***" is divided into two chapters.

First chapter of the thesis describes the desymmetrization of the *bis*-dimethyl amide **1** derived from tartaric acid with vinyl Grignard reagents and subsequent reduction of the resultant γ-keto amides **2a-c** to the γ-hydroxy amides **3a-c**. Application of the γ-hydroxy amides **3a-c** in the total synthesis of bio-active natural products such as gabosines, crassalactone C and anamarine is described in the subsequent sections.



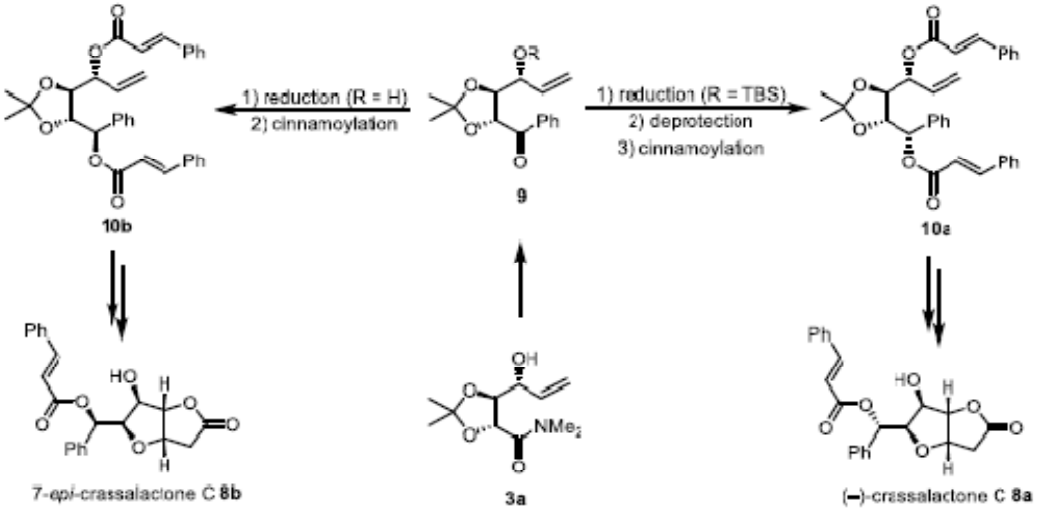
Scheme 1: *Synthesis of γ-hydroxy amides 3a-c derived from the desymmetrization of bis-dimethyl amide **1** of tartaric acid using vinyl Grignard reagents.*

In section A of the first chapter, application of the γ-hydroxy amides **3a-b** to the total synthesis of gabosine A **4**, gabosine F **5** and gabosine H **6** was described. Key strategy in the synthesis was the use of ring closing metathesis (RCM) reaction. Incidentally, the total synthesis of gabosine H **6** was not only accomplished for the first time but the synthesis also ascertained the absolute stereochemistry of the natural product. During the course of the synthesis of gabosine A **4**, an unprecedented formation of a unique 14-membered macrocycle **7** was observed. Incisive studies were conducted to elucidate the reaction sequence for the formation of the macrocyle **7**. It was found that the formation of the macrocycle **7** was through a tandem cross-metathesis/intramolecular hetero Diels-Alder reaction.



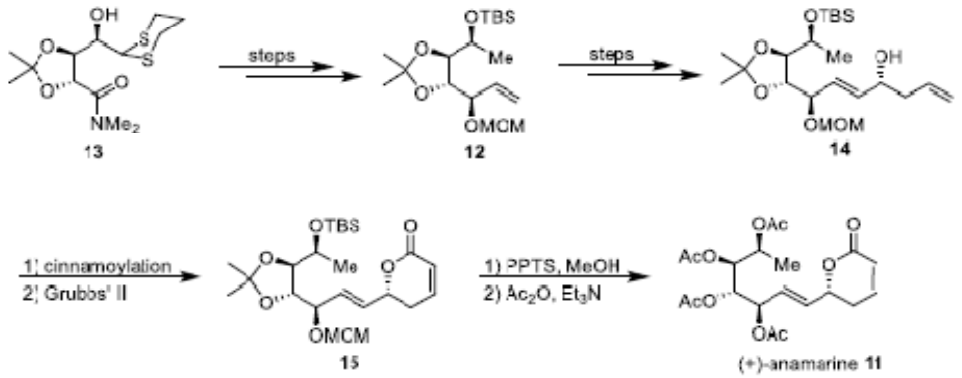
Scheme 2: *Application of the γ-hydroxy amides in the synthesis of gabosines 4-6 and a unique 14-membered macrocycle 7.*

Section B of chapter 1 delineated the utility of the γ-hydroxy amide **3a** in the total synthesis of (−)-crassalactone C **8a**. Crassalactone C **8a** is a cinnamoyl derivative of styryllactone natural product goniofufurone and was found to possess marginal in *vitro* cytotoxic activity. Pivotal strategies in the synthesis include the use of *bis*-cinnamoyl ester **10a** in the ring closing metathesis reaction which also evades the selective cinnamoylation of the benzylic hydroxy group.



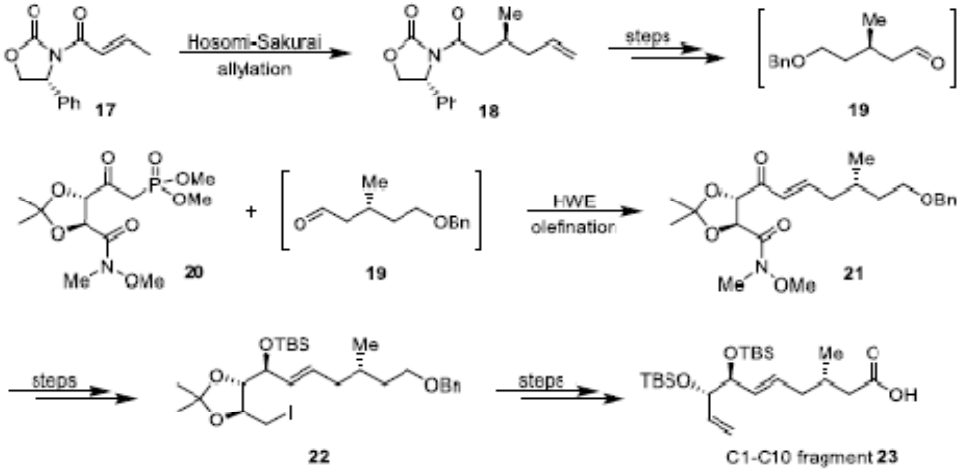
Scheme 3: *Stereoselective total synthesis of (−)-crassalactone C 8a and 7-epi-crassalactone C 8b.*

Section C of Chapter 1 deals with the total synthesis of (+)-anamarine **11**. While the γ-hydroxy amide **3a** was employed to synthesize an important intermediate **12** enroute to the synthesis of anamarine, to mitigate the number of steps in the synthesis, the γ-hydroxy amide **13** was employed for the synthesis of (+)-anamarine **11**. Key reactions in the total synthesis include the use of 1,3-dithiane as a surrogate for the methyl group, Brown's allylation and ring closing metathesis.



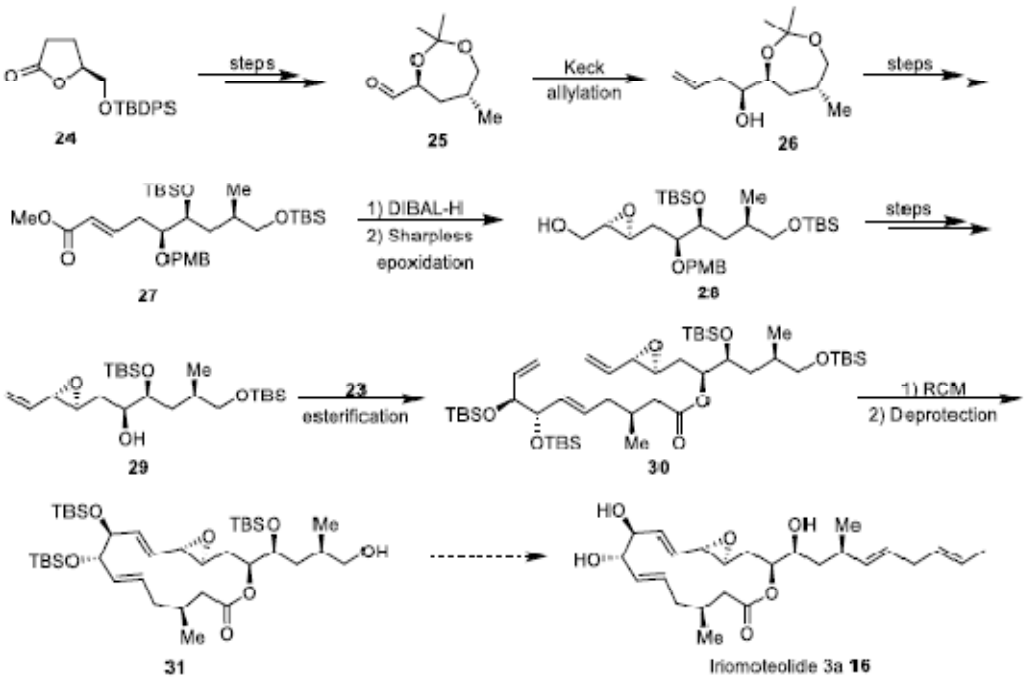
Scheme 4: *Total synthesis of (+)-anamarine* ***11****.*

In second chapter of the thesis, formal total synthesis of iriomoteolide 3a **16** is presented. Iriomoteolide 3a **16** is a unique 15-membered marine macrolide isolated by Tsuda's group from the *Amphidinium* strain HYA024, with impressive *in vitro* cytotoxic activity against human lymphoma cell line DG-75 (IC_{50} 0.08 μg/mL) and Raji cells (IC_{50} 0.05 μg/mL). Salient features of the synthesis include the synthesis of the chiral aldehyde **19** from the oxazolidinone **17** and the use of β-keto phosphonate **20** derived from D-(−)-tartaric acid in the Horner-Wadsworth-Emmons olefination reaction to construct the C1-C10 fragment **23** of iriomoteolide 3a **16**.



Scheme 5: *Synthesis of the C1-C10* ***23*** *fragment of iriomoteolide 3a* ***16****.*

Synthesis of the C10-C18 fragment **29** was accomplished from the butyrolactone **24** using Keck allylation and olefin cross metathesis reactions as key steps. Ring closing metathesis of the ester **30**, followed by selective deprotection of the primary TBS group afforded the key intermediate **31**, the transformation of which to iriomoteolide 3a **16** is known in literature.



Scheme 6: *Formal total synthesis of iriomoteolide 3a* ***16****.*